Remarks

Upon entry of the foregoing amendment, claims 40-60 are pending in the application, with claim 40 being the independent claim. Claims 1-39 have been cancelled without prejudice to or disclaimer of the subject matter therein. Support for claim 40 can be found, inter alia, at paragraphs 30 through 32. Support for claim 41 can be found, inter alia, at paragraph 45. Support for claims 42-43 can be found, inter alia, at paragraph 30. Support for claim 44 can be found, inter alia, at paragraph 39. Support for claim 45 can be found, inter alia, at paragraph 50. Support for claim 46 can be found, inter alia, at paragraphs 19-26 and Figures 8-15. Support for claims 47-50 can be found, inter alia, at paragraphs 67-70. Support for claim 51 can be found, inter alia, at paragraph 52. Support for new claims 52-60 can be found, inter alia at paragraphs 75-82.

As requested by the Examiner, Figure 4 of the specification has been amended to include SEQ ID NOs corresponding to the nucleotide sequences shown in the figure. Pursuant to 37 C.F.R. § 1.84(c), Applicants submit herewith a substitute drawing of Figures 3-4 labeled as "Replacement Sheet". A marked up version of Figure 4 indicating changes made is submitted herewith and labeled as "Annotated Marked-up Drawings".

The specification has also been amended to insert the Substitute Sequence Listing, submitted herewith, in order to include nucleotide sequences shown in Figure 4. In accordance with 37 C.F.R. § 1.821(f), the paper copy of the Substitute Sequence Listing and the computer readable copy of the Substitute Sequence Listing submitted

herewith in the above-captioned application are the same. In accordance with 37 C.F.R. § 1.821(g), this submission includes no new matter.

These changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and request that they be withdrawn. Applicants respectfully request that the application be deemed sufficient for allowance.

Objections to the Specification

The Examiner has objected to the specification as noted in (a)-(d) on page 2 of the Office Action. Paper No. 12. Applicants thank the Examiner for his suggestions regarding the objections provided in a telephone discussion conducted on December 30, 2003. Based on the Examiner's suggestions, Applicants provide the remarks below.

With regard to the comments in (a)-(d) below regarding nucleotide and/or amino acid disclosures in patent applications, Applicants note that nucleotide and/or amino acid sequences as used in 37 C.F.R. §§1.821-1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. 37 C.F.R.§ 1.821(a). Furthermore, amino acids are those L-amino acids commonly found in naturally occurring proteins and are listed in WIPO Standard ST.25 (1998), Appendix 2, Table 1. 37 C.F.R.§ 1.821 (a)(2).

a. With regard to the sequence identifier requested for page 4, paragraph 10, Applicants note that the modified gene described in paragraph 10 is part of a discussion

on background art and is not part of the claimed invention. Furthermore, four or more amino acids have not been specifically defined. Thus, sequence identifiers are not required.

With regard to the sequence identifier requested for page 13, paragraph 49, Applicants note that four or more amino acids have not been specifically defined. For the Examiner's convenience, Applicants have nevertheless amended the specification at paragraph 49 to include a sequence identifier for the full-length tissue plasminogen activator gene.

With regard to the sequence identifier requested for page 29, paragraph 100, Applicants note that four or more amino acids have not been specifically defined. The genes described in this paragraph are referred to by their names, and not by a listing of their amino acid sequences. Thus, sequence identifiers are not required.

b. The Examiner has noted several locations in the specification where sequences are identified by commercial database accession numbers (e.g. page 11, paragraph 40; page 15, paragraph ; page 20, paragraph 67; page 25, paragraph 87). In the telephone discussion with the Examiner, the Examiner noted that recitation of the accession numbers was acceptable. Accordingly, no changes regarding identification of database accession numbers have been made.

c. The Examiner has objected to Figure 4, stating that it "contains nucleic acid sequences which are not identified by sequence identification number . . ." Paper No. 12, page 2. Applicants have amended Figure 4 to include sequence identifiers where

appropriate. Applicants have also amended the sequence listing such that all sequences identified in Figure 4 have been included.

d. The Examiner has stated that the signal peptide OmpA and the protein gpIII "are not defined in the specification by a sequence identification numbers." Paper No. 12, page 2. Applicants note that sequence identifier numbers are only required when four or more amino acids residues are specifically recited in the specification. In this case, the proteins are referred to by name and not by a listing of amino acid residues. Therefore, no sequence identifier is required.

In the telephone discussion with Applicants, the Examiner has noted that the sequence identifier for OmpA be recited once, and that a sequence identifier for gpIII does not need to be provided. Applicants have thus amended the specification at the first recitation of OmpA on page 7, paragraph 30, to include the sequence identifier.

The Examiner has also noted that the specification contains nucleic acid and amino acid sequences which are described by sequence identifiers and recommends that Applicants delete the sequences from the specification and the claims. Paper No. 12, page 2. Applicants note that deletion of these sequences has been recommended, but not required. Accordingly, no changes regarding the recitation of nucleic acid and amino acid sequences in the specification has been made.

Based on the above remarks and the amendments to the specification, Applicants respectfully request that the above objections be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has objected to the specification and rejected claims 6 and 33 under 35 U.S.C. §112, first paragraph. Paper No. 12, page 3-4. The Examiner stated that "[t]he specification is objected to under 35 U.S.C. §112, first paragraph, as the specification lacks a sufficient written description for enablement based on deposit requirement." Paper No. 12, page 3. The Examiner further stated that claims 6 and 33 "are rejected under 35 U.S.C. §112, first paragraph, for the reasons set forth in the objection to the specification." Paper No. 12, page 4. Applicants respectfully disagree.

Applicants have cancelled claims 6 and 33 and added new claim 59 which recites the pComb3HSS phagemid.

According to the requirements for the deposit of biological material, the biological material need not be deposited, inter alia, if it can be made or isolated without undue experimentation. 37 C.F.R. § .802(b) (2003).

Based on the description of pComb3HSS in the specification and based on guidance in the art, Applicants argue that the specification contains adequate written description Furthermore, Applicants argue that the claims are sufficiently enabled and that a vector comprising pComb3HSS can be made without undue experimentation. The pComb3HSS phagemid was provided to the inventors of the present application by Dr. Carlos F. Barbas, Scripps Institute, USA. *See*, Specification, paragraph 90. The inventors of the current application utilized this vector to construct pComb3H-K2S. The pComb3H-K2S construct is a vector comprising pComb3HSS in that it is simply the pComb3HSS phagemid with the K2S sequence inserted into it. *See*, Specification,

paragraph 90. If one were to delete the K2S sequence from the pComb3H-K2S construct, the result would be the pComb3HSS phagemid. The deletion of the K2S insert can be easily performed by digestion with a restriction endonuclease using standard molecular biology cloning techniques.

The specification also discloses a map of a vector comprising pComb3HSS with K2S inserted into it. *See*, Specification, Figure 3. This map provides the locations of key elements of pComb3HSS such as the lac operon, the ribosomal binding site, the gpIII gene, and the ampicillin resistance gene. The regions which these elements span are indicated by the numbering of the nucleotide sequences within the vector. *See,* Specification, Figure 3. Thus, the specification provides disclosure sufficient for the claims to be enabled.

In addition, one skilled in the art could use disclosure in the specification coupled with disclosure in the art to make a vector comprising the pComb3HSS phagemid without undue experimentation. The vector comprising pComb3HSS can be made by modification of the pComb3 vector. The pComb3 vector is disclosed and described in "Assembly of combinatorial antibody libraries on phage surfaces: The gene III site, " Barbas, *et al.*, *Proc. Natl. Acad. Sci. USA 88*: 7978-7982 (1991) (cited as Document AT1 in the IDS filed April 23, 2002). The construction of pComb3 is described in detail in the "Materials and Methods" section. Barbas at 7978. This section indicates how the vector was cloned and what sources were used to obtain fragments which were ligated together to generate pComb3, the backbone utilized to construct the phagemid of the

claimed invention. Furthermore, the sequence of the pComb3 vector has been submitted to and can be easily retrieved from the public GenBank sequence database.

Finally, elements of the pComb3HSS phagemid are well known in the art. The sequences of these elements are readily available or can be made by one skilled in the art. One skilled in the art would know how to manipulate these elements using standard DNA techniques, together with the publicly available pComb3 vector backbone, to construct a vector comprising pComb3HSS.

Thus, based on the disclosure in the specification and in the art, one of skill in the art could make and use a vector comprising the pComb3HSS phagemid without undue experimentation. The disclosure provides a map diagramming the elements of pComb3HSS. Additionally, the elements of pComb3HSS were available in the art. One of skill in the art, using the information described above and standard cloning techniques in molecular biology, could readily make and use the recited vector comprising the pComb3HSS phagemid. Accordingly, Applicants assert that the specification contains adequate written description and the claimed invention is sufficiently enabled. Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-15, 17-24 and 31-37 under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Paper No. 12, page

4. Applicants respectfully traverse and request that the rejection under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Applicants will address the Examiner's rejections under 35 U.S.C. § 112, second paragraph, as (a)-(l) below in response to rejections (a)-(l) in the Office Action. Paper No. 12, page 4.

a. The Examiner has alleged that the following phrases render the respective claims indefinite: "a tPA variant" and "a K2S variant" in claims 1, 2, 4, 10, and 11; "or a functional derivative thereof" in claims 1, 2, 12, and 14; "or a variant due to the degenerate nucleotide code" in claims 7, 12, and 15; "functional variant thereof" in claims 7 and 15; "OmpA" in claims 1, 2, 4, 5, and 14.

Applicants have cancelled the above-listed claims and added new claims 40-60. Independent claim 40 recites "a tPA variant" and "a K2S variant". Applicants note that variants of tPA and K2S are specifically referred to and described in the specification. *See*, e.g., Specification, pages 10-11, paragraphs 39-41; page 15, paragraph 54; pages 16-17, paragraphs 56-58; page 20, paragraph 90; page 31, paragraph 104. For example, tPA variants include the finger domain, the growth factor domain, the kringle 1 domain, the kringle 2 domain, and the protease domain. *See*, Specification, paragraph 39. K2S variants include those disclosed in Figures 8-15 of the specification.

With regard to the phrases "or a functional derivative thereof", "or a variant due to the degenerate nucleotide code", and "functional variant thereof", Applicants note that these phrases are not included in newly added claims 40-60. The rejection is therefore rendered moot.

Finally, with regard to the phrase "OmpA", Applicants note that for reasons set forth above in the objections to the specification regarding sequence identifiers, a sequence identifier is not required to be provided next to a recitation of "OmpA" as it is simply the name of the gene and not a recitation of four or more specifically defined amino acid residues. *See*, 37 C.F.R.§ 1.821 (a).

b. The Examiner has stated that the phrases "DNA-derived" and "an active and correctly folded protein", render claim 1 indefinite. The Examiner states that the phrase "an active and correctly folded protein" is assumed to mean "a thrombolytically active and correctly folded protein. " Paper No. 12, page 4. Applicants have cancelled claim 1 and added new claims 40-60. New claim 40 recites the phrase "thrombolytically active protein."

c. The Examiner has rejected claims 1-3, and 5-14 as being incomplete. Paper No. 12, page 4. Applicants have cancelled claims 1-3 and 5-14. The rejection of these claims is therefore rendered moot.

d. The Examiner has alleged that the phrase "operably linked" in claim 1 renders the claimed method inoperable. Paper No. 12, page 4. The Examiner notes that the protein product of two operably linked DNA sequences "could be either a fusion protein or two different polypeptides." Paper No. 12, page 4.

Applicants have cancelled claim 1 and added claims 40-60. New claim 40 recites the phrase "operably linked". Applicants note that "operably linked" is specifically defined. *See*, Specification page 8, paragraph 32. "Operably linked" according to the specification, is defined in the context of DNA encoding the tPA, tPA variant, K2S

molecule or K2S variant which is cloned in close proximity to the OmpA DNA sequence in order to achieve expression of a fusion protein. *See*, Specification, page 8, paragraph 32. The phrase "operably linked" is defined. Accordingly, Applicants respectfully request that this rejection be withdrawn.

e. The Examiner has alleged that the phrases "DNA coding gpIII" in claims 4 and 5 and "gpIII protein" in claim 33 renders the claims indefinite Paper No. 12, page 5. Applicants note that for reasons set forth above in the objections to the specification regarding sequence identifiers, a sequence identifier is not required to be provided next to a recitation of "gpIII" as it is simply the name of the gene and not a recitation of four or more specifically defined amino acid residues. *See*, 37 C.F.R.§ 1.821 (a). Accordingly, no sequence identifiers are required.

f. The Examiner has alleged that the phrase "pComb3HSS phagemid" in claim 6 renders the claimed method "confusing and inoperable." Paper No. 12, page 5. Applicants have cancelled claim 6. Newly added claim 59 recites the pComb3HSS phagemid. Applicants refer the Examiner to the remarks above in the section "Rejections under 35 U.S.C. § 112, first paragraph." Based on these remarks, Applicants assert that the phrase "pComb3HSS phagemid" is definite and respectfully request that this rejection be withdrawn.

g. Claims 7-9 are cancelled. The rejections of these claims are therefore rendered moot.

h. The Examiner has alleged that absence of sequence identifiers in claims 11 and 17-20 render these claims indefinite. Applicants have cancelled the above-listed claims and inserted sequence identifiers in newly added claims 40-60 where appropriate.

i. The Examiner has alleged that the phrase "a functional variant thereof or variant due to the degenerate nucleotide code" in claim 15 renders this claim indefinite. Claim 15 is cancelled. The rejection of this claim is therefore rendered moot.

j. The Examiner has alleged that the phrase "operably linked" in claims 2 and 14 render these claims indefinite. Applicants have cancelled claims 2 and 14. Newly added claim 40 recites the phrase "operably linked". Applicants refer the Examiner to the remarks above in section (d) regarding this rejection. Based on these above remarks, Applicants assert that the phrase "operably linked" is definite and respectfully request that this rejection be withdrawn.

k. The Examiner has alleged that the phrase "hybridizing under stringent conditions" in claims 21 and 23 renders these claims indefinite. Applicants have cancelled claims 21 and 23. New claim 53 recites the phrase "hybridizing under stringent conditions" and further recites specific hybridization conditions corresponding to "a hybridization carried out in 6x SSC, 5x Deinhardt's solution, and 0.1 SDS% at 65°C." Applicants assert that claim 53 is now definite and respectfully request that this rejection be withdrawn.

l. Claims 22, 24, 31, 32, and 34-37 have been cancelled. The rejections of these claims are therefore rendered moot.

All of the rejections under 35 U.S.C. § 112, second paragraph, have been addressed or rendered moot. Accordingly, Applicants respectfully request that the above rejections be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1, 3, 8-10, 14, 21-23, 31, 32, and 34-37 under 35 U.S.C. § 102(b) as allegedly being anticipated by Georgiou, *et al.* (U.S. Patent No. 6,027,888). Paper No. 12, page 6. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). MPEP § 2131.

Applicants assert that the present claims are not anticipated by Georgiou, *et al.* Georgiou, *et al.* disclose a nucleic acid sequence encoding human tPA fused to an OmpA signal peptide. Applicants have cancelled claims 1, 3, 8-10, 14, 21-23, 31, and added claims 40-60. New claims 40-60 are directed to a DNA molecule comprising: (1) a sequence encoding tPA, K2S, or a variant thereof; (2) a sequence encoding the OmpA signal peptide; *and*; (3) the sequence encoding either the signal peptide sequence SEGN or SEGNSD. Georgiou, *et al.* do not disclose a nucleic acid molecule comprising a sequence which encodes either the peptide SEGN or SEGNSD. Because Georgiou, *et al.* do not disclose every element of claims 40-60, these claims are not anticipated by Georgiou, *et al.*

In addition, Georgiou, *et al.*'s claimed invention is directed to *coexpression* of both tPA and a disulfide isomerase protein. Columns 63-66. Georgiou, *et al.* do not

disclose the expression of tPA alone. Georgiou, *et al.* note that many proteins cannot be efficiently expressed in bacterial hosts due to the failure of disulfide bond formation, critical in some proteins for proper folding and for transport and secretion. Column 2, lines 18-11.

Georgiou, *et al.*'s invention requires expression of a first DNA segment encoding a disulfide isomerase and a second DNA segment encoding a eukaryotic polypeptide, such as tPA. Column 4, lines 20-54. Georgiou, *et al.* do not anticipate an invention where a bacterial host expresses a properly folded tPA, without expression of a disulfide isomerase.

Applicant's claimed invention does not require expression of disulfide isomerase. Thus, the claimed invention is not anticipated by Georgiou, *et al.* Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1-3, 7-24, 31, 32, and 34-37 under 35 U.S.C. § 103 as allegedly being unpatentable over Raymond, *et al.* (EP 0357391 A2) in view of Obukowicz, *et al. (Biochemistry 29*: 9737-9745 (1990), Niwa, *et al.* (U.S. Patent No. 5,840,533) and the nucleic acid encoding human tissue plasminogen activator. Paper No. 12, page 7. Applicants point out that the first inventor of EP 0357391 A2, referred to above, is Raymond Wong. Applicants thus refer to EP 0357391 A2 as Wong, *et al.*

In order to establish a *prima facie* case of obviousness, the references, when combined, must teach or suggest all the claim limitations. MPEP § 2143. Based on the arguments below, Applicants assert that the pending claims are not rendered obvious in view of the above-listed references.

New claims 40-60 are generally directed to a DNA molecule comprising: (1) tPA, K2S, or a variant thereof; (2) OmpA and; (3) either the signal peptide sequence SEGN or SEGNSD; where prokaryotic host cells transformed with the DNA molecule secrete the tPA, K2S, or variant thereof, extracellularly as a thrombolytically active protein.

Wong, *et al.* disclose an expression system in *E. coli* where a heterologous protein is fused in frame to a nucleic acid sequence encoding the OmpA signal peptide. Wong, *et al.*, however, do not teach or suggest expressing a nucleic acid sequence comprising tPA, K2S, or a variant thereof. Wong, *et al.* also do not teach or suggest a DNA molecule comprising a sequence encoding the peptide SEGN or SEGNSD.

Obukowicz, *et al.* teach expression of a fusion construct comprising the signal peptide PhoA and the K2S protein. Obukowicz, *et al.* do not teach or suggest a DNA molecule comprising a sequence encoding the peptide SEGN or SEGNSD. Thus Obukowicz, *et al.* do not rescue the deficiencies of Wong, *et al.*

The Examiner has stated that Niwa, *et al.* disclose variants of human tPA, one of which includes the peptide SEGNSD fused to the N-terminus of K2S. Paper No. 12, page 8. The studies of Niwa, *et al.* analyze variants of tPA in terms of activity to determine which variants are more active than their corresponding wild-type tPA. Niwa,

et al. do not teach or suggest using these variants in a fusion construct with a signal peptide sequence, such as OmpA, and do not discuss the secretion of these variants either into the periplasmic space or the extracellular culture medium. Thus, Niwa, *et al.* also do not cure the deficiencies of Wong, *et al.*

The known nucleic acid sequence encoding human tissue plasminogen activator also does not rescue the deficiency of Wong, *et al.* as it merely teaches the sequence of human tPA, and does not provide any suggestion for a nucleic acid sequence encoding tPA to be operably linked to the signal sequence OmpA or the sequence encoding either the peptide SEGN or SEGNSD.

Wong, *et al.* in view of in view of Obukowicz, *et al.,* Niwa, *et al.* and the nucleic acid encoding human tissue plasminogen activator do not render claims 40-60 obvious as they do not teach or suggest all of the limitations of the claims. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

The Examiner also has rejected claims 11, and 17-20 under 35 U.S.C. § 103 "as being unpatentable over Georgiou, *et al.* in view of Obukowicz, *et al.* and the nucleic acid encoding human tissue plasminogen activator. Paper No. 12, page 9.

As discussed above, new claims 40-60 are directed to a DNA molecule comprising: (1) a sequence encoding tPA, K2S, or a variant thereof; (2) a sequence encoding the OmpA signal peptide; *and*; (3) the sequence encoding either the signal peptide sequence SEGN or SEGNSD.

Georgiou, *et al.* do not disclose a nucleic acid molecule comprising a sequence which encodes either the peptide SEGN or SEGNSD. Obukowicz, *et al.* teach expression of a fusion construct comprising the signal peptide PhoA and the K2S protein, but do not teach or suggest the use of the SEGN or SEGNSD peptide as part of the fusion construct. The sequence encoding human tissue plasminogen activator merely teaches the sequence of human tPA and does not teach or suggest the use of SEGN or SEGNSD peptide as part of the fusion construct. Thus, neither Obukowicz, et al. nor the sequence encoding human tPA rescue the deficiency of Georgiou, *et al.*

Georgiou, *et al.* in view of Obukowicz, *et al.* and the nucleic acid encoding human tissue plasminogen activator do not teach or suggest all of the limitations of the claims. Thus, Applicants respectfully request that this rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

Provisional Double Patenting Rejection

The Examiner has provisionally rejected claim 6 under 35 U.S.C. § 101 as claiming the same invention as that of claim 8 of copending Appl No. 09/987,457. Paper No. 12, page 10. Furthermore, the Examiner has provisionally rejected claims 1-5, 7-24 and 31-37 under the judicially created doctrine of obviousness-type double patenting over claims 1-7 and 9-11 of copending Appl No. 09/987,457. Paper No. 12, page 10. Applicants have cancelled claims 1-5, 6, 7-24 and 31-37. Thus, the provisional double patenting rejection has been rendered moot. Reconsideration and withdrawal of the provisional rejection are respectfully requested.

Conclusion

Prompt and favorable consideration of this Amendment is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,
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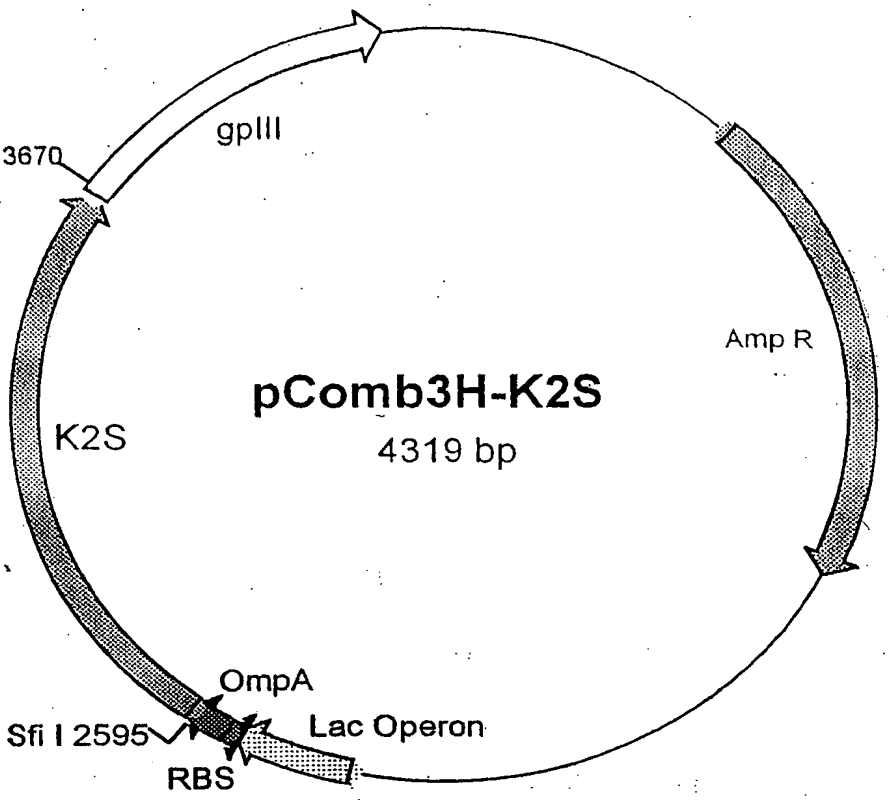
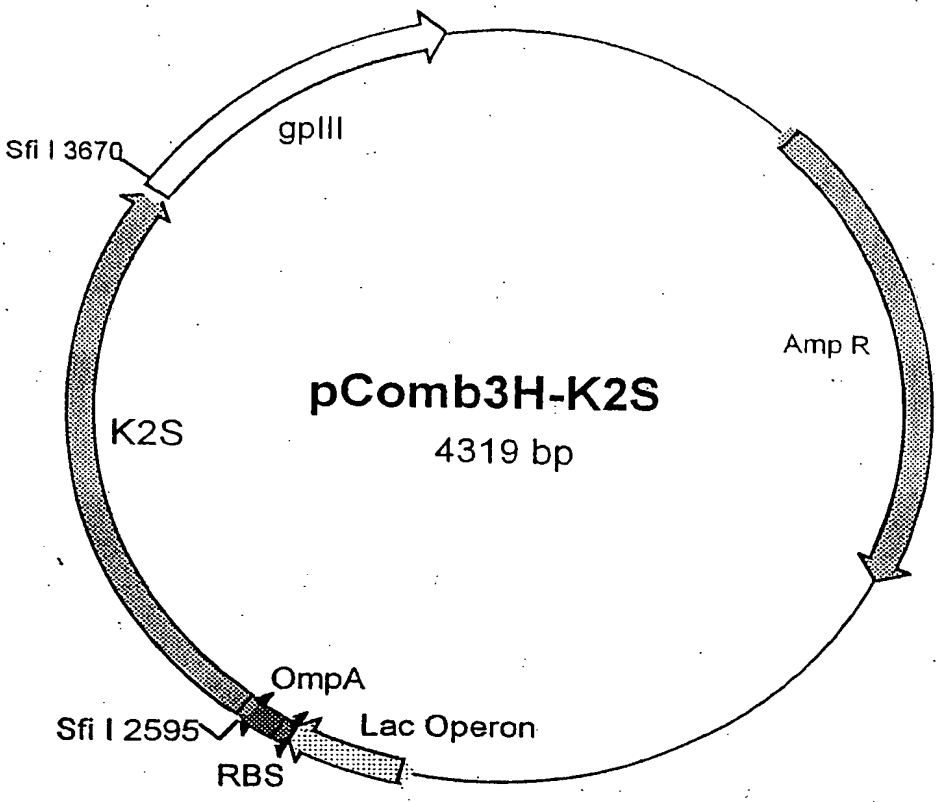


Lac operon	2316-2513
RBS	2514-2533
Omp A	2534-2599
K2S	2600-3664
gp III	3665-4219
Amp R	515- 1394

Figure 3

3′-TGTACGCTGGCACTGTCCGGCCGGTC-5′ MAsTPA (SEQ ID NO: 25)
TTCGTGACAACATGCGACCGGGCCAGGCCGGCCAGGAGGGTGGT
<*K2S* gene gpIII gene> (SEQ ID NO: 26)
AAGCACTGTTGTACGCTGGCCCGGTCCGGCCGGTCCTCCCACCA
5′-ACATGCGACCGTGACAGGCCGGCCAG-3′ MsTPA (SEQ ID NO: 24)

Figure 4



Lac operon	2316-2513
RBS	2514-2533
Omp A	2534-2599
K2S	2600-3664
gp III	3665-4219
Amp R	515- 1394

Figure 3

3′-TGTACGCTGGCACTGTCCGGCCGGTC-5′ MAsTPA (SEQ ID NO: 25)
TTCGTGACAACATGCGACCGGGCCAGGCCGGCCAGGAGGGTGGT
<K2S gene
gpIII gene> (SEQ ID NO: 26)
AAGCACTGTTGTACGCTGGCCCGGTCCGGCCGGTCCTCCCACCA
5′-ACATGCGACCGTGACAGGCCGGCCAG-3′ MsTPA (SEQ ID NO: 24)

Figure 4